REMARKS

I. STATUS OF THE CLAIMS

Claims 3 and 23-24 are cancelled without prejudice or disclaimer to the subject matter therein. Applicants reserve the right to file one or more continuing applications to the canceled subject matter. Claim 1 is amended to incorporate the subject matter of claim 3, *i.e.*, to recite the concentration of the high molecular weight rate controlling polymer as being "from about 5 to about 95% (w/w)." Claim 4 is amended to depend from claim 1, given the cancellation of claim 3 herein. Finally, claims 37, 41, 45, and 49 are amended to delete the recitation of trademarked terms, namely Tetronic 1508® (replaced with the generic term "poloxamine 908") and Crodestas SL40®.

Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested. Following entry of these amendments, claims 1, 2, 4-22, and 25-54 are pending.

II. TRADEMARKS RECITED IN THE CLAIMS

Claims 37, 41, 45, and 49 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for reciting the trademarks "Tetronic 1508®" and "Crodestas® SL-40." Office action at page 2. The Office states that these trademarks cannot be used to identify any particular material or product, but only to identify the source of the goods, not the goods themselves. *Id.* Since the trademarks are used to identify the surface stabilizer "the identification/description is indefinite." *Id.*

Applicants have deleted the term "Tetronic 1508" and replaced it with the generic term for this chemical compound, poloxamine 908. In addition, the term "Crodestas® SL-40" has been deleted from the claims. Accordingly, this ground for rejection is moot.

III. REJECTION OF THE CLAIMS UNDER 103(a): CLAIM 1 INCORPORATES THE SUBJECT MATTER OF CLAIM 3, WHICH IS NOT REJECTED, AND THEREFORE THE REJECTION IN LIGHT OF DESIENO, LIVERSIDGE, AND MODY IS MOOT

Claims 1, 2, 8-22, 25-31, and 34-53 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,573,783 ("Desieno"), in view of U.S. Patent Nos. 5,145,684 ("Liversidge"), and 5,853,756 ("Mody"). Office action at page 3. Applicants respectfully traverse this ground for rejection.

The Office admits that Desieno "does not expressly teach the time period of controlled release from 2 to about 24 hours"; "does not explicitly teach the [recited] particle distribution"; and "does not expressly teach the concentration of the rate-controlling polymer, the binder, and the lubricant." See the Office action at pages 4 and 5.

Without acquiescing to the Office's point of view, Applicants have incorporated the subject matter of present claim 3 into claim 1. **Claim 3 has not been rejected in this particular 103(a) rejection.** See page 3, line 7 ("Claims 1, 2, 8-22, 25-31 and 34-53 are rejected"). It therefore follows – from the rationale underlying the Office's rejection – that the recitation of the concentration of the high molecular weight rate controlling polymer as being "from about 5 to about 95% (w/w)" is *per se* non-obvious in light of the combination of Desieno, Liversidge, and Mody.

Accordingly, Applicants respectfully request that the rejection of claims 1, 2, 8-22, 25-31, and 34-53 in light of Desieno, Liversidge, and Mody, be withdrawn.

IV. REJECTION OF THE CLAIMS UNDER 103(a): THE PRIOR ART, PARTICULARLY "FRIEND," TEACHES AWAY FROM CONTROLLED RELEASE DRUG FORMULATIONS

Claims 3-7, 32, 33, and 54 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Desieno (*supra*), in view of Liversidge (*supra*) and Mody (*supra*) and U.S. Patent No. 5,811,388 ("Friend"). Office action at page 5. Applicants respectfully traverse this ground for rejection.

A. The Office's Basis for the Rejection is Flawed

The Office relies on Friend to cure Desieno's failure to teach "the concentration of the rate-controlling polymer, the binder, and the lubricant." According to the Office, Friend teaches "excipients . . . at a level from about 2-50% [which further include] HPMC, PVP, and cellulosic derivatives" and that the polymeric enteric coating is a Eudragit polymer "in an amount of from about 0.5 to 10%." Thus, "it would have been obvious . . . to modify the nanoparticle of Desieno and Liversidge using the excipients and the enteric coating polymers in an effective amount in view of [Friend], because Friend teaches a tablet dosage form suitable for controlled release of poorly soluble drug[s]." *Id.* at page 6. The Office predicts that "the expected result would [be] a controlled release film matrix coated carrier that exhibits excellent bioavailability and [is] extremely stable." *Id.*

Applicants respectfully reiterate that the presently claimed nanoparticulate compositions are specifically designed to prevent rapid dissolution of the drug and to control the release of the formulated drug by way of a rate-controlling polymer. By contrast, Desieno fails to teach or suggest a *rate-controlling polymer* integrated in a rate-controlling matrix with the drug composition, or coating the nanoparticulate drug composition, as recited in the claimed invention; Liversidge teaches away from controlled release formulations; and Friend teaches delayed release of a drug targeted for the lower gastrointestinal tract.

B. Friend Teaches Delayed Release, and not Controlled Release, Compositions

In this respect, whether or not Friend teaches a particular effective concentration amount of excipient is irrelevant because the skilled person, for the reasons outlined below, would not have been motivated to modify one of the other prior art formulations with Friend's excipient for delayed and regional release, because she would not have expected the excipient in that other pharmaceutical context to have worked as intended. That is, Friend specifically teaches that its compositions are *delayed release* compositions especially formulated for dispersion in the lower GI, and explicitly distinguishes those compositions from sustained or extended release compositions:

> The compositions and methods of this invention are of a delayed release nature (as compared to sustained or extended release). Thus, for purposes of this application a delayed release composition allows for the release of most of the active ingredient in the lower GI, particularly the colon without releasing any significant amount of the drug in the upper GI tract as the composition travels through the entire GI tract. ***This is different*** than a sustained release composition that releases the active on a regular (i.e. constant) basis throughout the GI.

Emphasis added; see col. 4, line 66 to col. 5, line 6.

Accordingly, Friend teaches *away* from rate-controlled nanoparticulate formulations. Friend requires a delayed release formulation such that the tablet does not disintegrate until it physically reaches the lower GI tract. This is because dispersion of the formulated drug in the upper GI tract would expose the drug to enzymatic degradation, thereby inactivating it (col. 4, lines 60-66). Accordingly, Friend requires a formulation that includes excipients "to provide the composition with the desired delayed release/regional delivery characteristics" (col. 11, lines 38-42).

C. Desieno and Liversidge are Both Directed to Immediate Release Compositions

Desieno and Liversidge both teach the polar opposite of Friend. Liversidge and Desieno teach *immediate* release drug nanoparticulate compositions. They do not teach or suggest controlled release nanoparticulate compositions. In fact, Liversidge teaches ***against*** controlled release nanoparticulate compositions, because Liversidge teaches that the aim of controlling the size and the size range of drug particles is *to increase the rate of dissolution, and thus to increase the release rate of the nanoparticulate drug. See* col. 1, lines 28-35:

> the rate of dissolution of a particulate drug can increase with increasing surface area, i.e., decreasing particle size. Consequently, methods of making finely divided drugs have been studied and efforts have been made to control the size and size range of drug particles in pharmaceutical compositions. For example, dry milling techniques have been used to reduce particle size and hence influence drug absorption

The point in Liversidge therefore was to produce "drug particles having an extremely small effective average particle size" to thereby enhance the rapidity of drug dissolution over a period of time. Liversidge at column 3, lines 15-20. The Office only relied on Liversidge, in any event, to explain what is meant by "average particle size" and not to characterize some feature that is unique to rate-controlled drug formulations. See the Office action at page 5.

Furthermore, "excipient" in Liversidge is a surface modifier that is present in an amount to prevent the drug particles from "flocculate[ing] or agglomerate[ing]." Id. "Flocculate" is the verb form of "flocculent" which means "containing, consisting of, or occurring in the form of loosely aggregated particles." MIRRIAM-WEBSTER ONLINE DICTIONARY (www.merriam-webster.com/dictionary/flocculent). Accordingly, Liversidge's surface modifier excipients prevent drug particles from clumping together, which would otherwise destroy the desired immediate-release properties of the formulation. The excipient of Friend, however, is present in an amount "sufficient to provide the composition with the desired delayed release/regional delivery characteristics, hardness rating, and handling characteristics" (col. 11, lines 38-41). That is, Friend's excipients necessarily prevent dispersion of the drug ("The compositions and methods of this invention are of a delayed release nature (as compared to sustained or extended release) . . . This is different

than a sustained release composition that releases the active on a regular (i.e. constant) basis throughout the GI"; col. 4, line 66 to col. 5, line 6). The two classes of excipients therefore (Liversidge's and Friend's) are at polar extremes of the spectrum: one class of excipients is used to facilitate rapid dispersion, the other class is used to prevent rapid dispersion.

D. There is no Motivation to Combine the Cited References

With this in mind, it becomes evident that when the teachings of the pertinent prior art are viewed as a whole, there is no way that the skilled person would have been motivated to modify the nanoparticles of Desieno and Liversidge using Friend's excipients in the amounts the Office suggests. There is no expectation of success at all. That is, contrary to the Office's position, the skilled person would not have expected a result evidencing "a controlled release film matrix coated carrier that exhibits excellent bioavailability and [is] extremely stable." Office action at page 6. Applicants do not know how the Office can make such conclusory descriptive statements ("*excellent* bioavailability"; "*extremely* stable," emphases added), about a hypothetical combination of ingredients taught in disparate prior art documents. Nevertheless, the cited prior art as a whole fails to disclose or suggest the unexpected pharmacokinetic properties of the nanoparticulate compositions of the present invention.

E. The Patent Office must consider Applicants' declaratory evidence of record in determining obviousness

Applicants have pointed these distinctions out to the Patent Office on numerous occasions and in numerous declarations during the course of prosecution and take this opportunity to relate the Federal Circuit's decision in In re Sullivan (Fed. Cir., case no. 2006-1507) (2007) ("Sullivan"), which dealt with a case where the Board of Patent Appeals and Interferences failed to consider appellants' submitted evidence. For that reason, the Court found the Board "committed error." The Court stated that "declarations . . . purport to show an unexpected result from use of the claimed composition, **how the prior art taught away from the composition**, and how a long-felt need existed for a new [ ] composition" (emphasis added).

Furthermore, the Court said that it was improper for the Board and Director of the PTO not to consider the importance of the **intended use** of appellants' composition. Indeed, the Court's position is consistent with its established precedent that dependence upon a

preamble phrase for antecedent basis may properly qualify a claim's scope because it indicates a reliance on the preamble and the body to define the invention, see Eaton Corp v Rockwell Int'l Corp., 323 F.3d 1332, 1339 (Fed. Cir. 2003) ("when the claim drafter chooses to use both the preamble and the body to define the subject matter of the claimed invention, the invention so defined, and not some other, is the one the patent protects").

In the present case, the intended use of Applicants' claimed invention is for producing controlled release drug formulations, as reflected by the preamble of claim 1 ("solid dose controlled release nanoparticulate composition"). Similarly, when a preamble is relied upon during prosecution to distinguish a claimed invention over the prior art, or the intended use is clear from the specification, then the preamble is transformed into a claim limitation because such reliance indicates the use of the preamble to define, in part, the claimed invention, see Catalina Mktg Int'l v Coolsavings.com, Inc. 289 F.3d 801, 808 (Fed. Cir. 2002).

Despite this precedent, the BPAI Director in Sullivan submitted that "the Board did consider the declarations and correctly gave them no weight because they only relate to the use of the claimed composition." The Court, however, responded that "the Board improperly failed to consider the rebuttal evidence" and that the Director's argument that appellants' "evidence only relates to use of an obvious composition" is "incorrect."

The Sullivan Court found "three pieces of evidence" that rebutted a *prima facie* finding of obviousness: (1) an expert declaration that described the state of the prior art which taught away from the claimed invention, (2) an inventor declaration concerning unexpected results, and (3) a second inventor declaration attesting to other unpredictability in the art. The Board "must consider such evidence," said the Court. By focusing on the intended use of the claimed composition, the Board "misse[d] the mark." The Court concluded that "the issue here is not whether a claim recites a new use, but whether the subject matter of the claim possesses an unexpected use."

Applicants submit that the remarks and declarations of record in the present application clearly show that the person of ordinary skill in the art would not have expected a poorly soluble nanoparticulate drug, surface stabilizer, and a high molecular weight rate-controlling polymer to yield a controlled release nanoparticulate composition that disperses the formulated drug for a time period ranging from about 2 to about 24 hours, as claimed.

F. No Combination of the Prior Art Teaches High Molecular Weight Rate-controlling Polymers as used in the Presently Claimed Drug Formulations

With regard to that latter point of the preceding subsection, Applicants previously amended the claims to specify that the rate-controlling polymers are high molecular weight polymers. As stated above, support for the amendment to the claims may be found, *inter alia*, in the examples of the disclosure. Example 2 in the specification, for example, provides a controlled-release nanoparticulate naproxen formulation using a mixture of Klucel and PVP as controlled-release polymer. The PVP used in the Example is Plasdone K-90. Plasdone K-90 has an average molecular weight of 1,300,000 (*see* Physical and Chemical Properties of Plasdone Povidone, attached as Exhibit A). In addition, all other polymers used in the examples in the application, such as Klucel and Methocel, also have a high molecular weight. Thus, Klucel has an average molecular weight between 80,000 and 1,150,000 (see Klucel, attached as Exhibit B), Methocel 4M has an average molecular weight of 95,000 (*see* Baumgartner *et al. Pharmac. Res. 19(8)*: 1084-90 (2002), attached as Exhibit C), and Methocel E4M has an average molecular weight of 86,000 (*see* Shah and Donovan *AAPS PharmSciTech 8 (2)*, Article 32, attached as Exhibit D).

In contrast to Applicants' claimed invention, Desieno discloses PVP/PEG polymers having an average molecular weight of 7,000 at the most, and describes polyethylene glycols having average molecular weights in the range of 300 to 8,000, with polyethylene glycol 3350 being the preferred PEG of the invention. *See* col. 5, lines 22-25. Thus, the Povidone (k15/17) used in Example 3 of Desieno, for example, has an average molecular weight of 10,000 (see Exhibit A appended to Applicants' RCE submission).

As stated in the Reply filed on February 12, 2007, it is well known in the art that the presence of polyethylene glycols having low average molecular weight, such as an average molecular weight in the range of 300 to 8,000, in drug formulations causes a fast drug dissolution rate, because the polymer is in a fluid state and maintains the fluidity of the drug composition when water is imbibed into the drug matrix. In contrast, high molecular weight polymers, such as high molecular weight polyethylene glycols, high molecular weight PVP, high molecular weight plant exudates or enteric polymers, such as those used in the present application, after imbibing water tend to be viscous and less fluid, thus slowing the drug dissolution rate and providing controlled release of the component drug.

This is contrary to the Office's opinion that it "relied on well known facts" to teach that "*very* high molecular weight starts from about 10,000" (emphasis in original), and that therefore "Desieno suggests the use of PVP having molecular weight that falls within the [recited] range." Office action at pages 7-8.

The prior art does not teach rate-controlling polymers that have a high molecular weight, as evidenced by the species of polymers used by Applicants to formulate the claimed drug compositions.

For all of these reasons, Applicants respectfully assert that claims 3-7, 32, 33, and 54 are not rendered obvious over the combination of the cited art and respectfully request withdrawal of this rejection.

CONCLUSION

Applicants believe that all of the stated grounds of rejections have been properly traversed or rendered moot. Therefore, the present application is now in condition for allowance. Favorable reconsideration of the application is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16 1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19 0741.